

A pediatric case of cystinuria diagnosed after nephrectomy

A pediatric case of cystinuria

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Abstract

Cystinuria is a disease characterized by impaired reabsorption of cystine and other dibasic amino acids. In this paper, we report a case diagnosed with cystinuria after multiple surgical interventions. A 16-year-old girl with a history of recurrent kidney stones admitted to Pediatric Nephrology Clinic. Her medical history revealed kidney stones detected at the age of one year, after that she had multiple surgical interventions, including nephrectomy. Direct microscopic examination of the urine revealed cystine crystals. Cystinuria was considered due to positive urinary cystine and dibasic amino acid excretion. She was recommended dietary sodium restriction and hydration. The patient was followed up without the formation of new kidney stones after the 12th month of her treatment. The etiology of the stone should be investigated in patients with recurrent urinary stones. Chronic kidney disease and associated morbidity and mortality can be prevented in patients with regular follow-up and treatment that will prevent stone formation.

Keywords

Cystinuria; Urolithiasis; Nephrolithiasis

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Introduction

Urolithiasis is a rare condition in childhood. However, its frequency has been increasing in recent years due to changes in lifestyles and eating habits. The prevalence and etiology of childhood stone disease are affected by such reasons as race and geography. The gender distribution varies in populations. Some publications reported equal prevalence in both genders, while others reported an increased risk for male sex. The prevalence of cystinuria is approximately 1: 10000 worldwide and also varies in populations [1]. Our country is located in the stone belt due to its geographical location and climate. A study from Turkey reported the prevalence of cystinuria as 1: 2155 [2]. A metabolic abnormality can be detected in nearly half of children with urolithiasis. The most common detected metabolic abnormalities are hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, and hyperuricosuria [3].

Cystinuria is an autosomal recessive disease characterized by impaired reabsorption of cystine and other dibasic amino acids (ornithine, lysine, and arginine) from the proximal tubule and the intestinal tract. The prevalence of cystinuria is approximately 1: 10000 worldwide and also varies in populations. The disease is caused by mutations in SLC3A1 and SLC7A9 genes. Detecting cystine crystals in direct urine examination is pathognomonic, and increased excretion of cystine in the urine is diagnostic. The only clinical manifestation of cystinuria is recurrent kidney stones and cystinuria constitutes 6-8% of childhood kidney stones. Because of low solubility in the physiological urine pH, cystine crystallizes and causes the formation of kidney stones. Chronic renal failure and hypertension are more common in patients with cystinuria than other types of kidney stones. Patients with late diagnosis or those left untreated are at risk for recurrent kidney stones, renal failure, and hypertension [1]. In this paper, we report a case that has been diagnosed with cystinuria after multiple surgical interventions including nephrectomy.

Case Report

A 16-year-old girl with a history of recurrent kidney stones admitted to Ege University Pediatric Nephrology Clinic due to nephrolithiasis. Her medical history revealed that kidney stones were detected at the age of one year, but she did not have a follow-up until 9 years of age. After that, she had 4 percutaneous nephrolithotomy (PNL) and 2 extracorporeal shock wave lithotripsy (ESWL) operations. The patient underwent a right nephrectomy due to a non-functional, atrophic right kidney at the age of 10. There was a 1st-degree cousin marriage between mother and father, in her family history. It was learned that her brother, father, and grandmother also had a history of kidney stones. On physical examination, her height was 147 cm (SD: -2.63), weight: 51,8 kg (SD: -0.7), heart rate: 78/min, blood pressure: 110/53 mmHg (normotensive). There were no pathological features except the operation scar on her abdomen. The results of the laboratory examination were as follows: hemoglobin:12.5 g/dL (RA: 11.7-15.3), white blood cells:10300/microL (RR: 4.1-11.0/microL), platelets: 277000/microL (RR: 150000-450000), urea:36 mg/dL (10-50 mg/dL), creatinin:0.6 mg/dL (RR: 0.6-1.1 mg/dL), uric acid: 4.1 mg/dL (RR: 2.6-6 mg/dL), sodium: 139 mg/dL (RR:

136-145 mg/dL), potassium: 4.5 mg/dL (3.5-5 mg/dL), calcium: 9.8 mg/dL (RR: 8.6-10.2 mg/dL), phosphorus: 3.3 mg/dL (RR: 2.8-5.5 mg/dL), magnesium 1.8 mg/dL (RR: 1.5-2.6 mg/dL), SGOT: 25 U/L (RR: <31 U/L), SGPT: 42 (RA: <34 U/L), ALP: 82 U/L (RR: 47-119 U/L), GGT:16 (RA: <38 U/L), parathormone: 45.69 pg/mL (RR:11-67 pg/mL), 25 hydroxy vitamin D: 48 ng/mL (RR:10-80 ng/mL). Patient's eGFRcreatinine value was 107 ml min/1.73m2, urinalysis: pH: 6.5, density: 1020 g / mL, in the direct microscopic examination, 2-3 leukocytes, cystine crystals, and epithelial cells were seen. The protein/creatinine ratio in spot urine was 0.15. Calcium (calcium/creatinine 0.20 mg/mg), uric acid (uric acid/creatinine: 0.20 mg/mg) and oxalate excretions (oxalic acid/creatinine: 40 mmol/mol creatinine) were in the normal range according to her age. Hypocitraturia [(Spot urine citric acid/creatinine: 209 mmol/mol creatinine) (RR: 300-400 mmol/mol creatinine)] was detected. Urine amino acid analysis revealed an increase in cystine, lysine, ornithine, and arginine excretion [lysine: 9575.9 mmol/mol creatinine (RR: <150 mmol/mol creatinine), ornitine:3609.2 mmol/mol creatinine (RA: <150 mmol/mol creatinine), arginine: 6421 mmol/mol creatinine (RR: <150 mmol/mol creatinine)]. Urine nitroprusside test was positive, and urine cystine excretion was 0.322 mmol/mol creatinine (RR: 0.01 <mmol / mol creatinine). On renal ultrasound (USG), the right kidney was absent due to the nephrectomy. Multiple lower pole stones of 12 mm and 14 mm size and medullary nephrocalcinosis were observed on the left kidney. Focal dilatation was also present in the renal pelvis and in some calyces. Renal CT imaging also showed multiple stones in the patient. In the image, 14 mm left-sided kidney stone with an absence of right kidney is seen (Figure 1). Cystinuria was considered in the patient due to the positive urinary cystine and dibasic amino acid excretion, as well as due to an accompanying recurrent stone history and family history. The genetic test revealed a SLC3A1 c833T> C (p.F278S) homozygous mutation. The patient was recommended dietary sodium restriction and necessary hydration. Potassium citrate treatment was started in order to provide urinary alkalization. The patient was followed up without the formation of new kidney stones after the 12th month of her treatment. The informed consent for the publication was obtained from the patient and her caregiver.



Figure 1. Renal CT showing 14 mm sized left kidney stone with an absence of right kidney.

Discussion

Cystinuria is an absorption disorder of dibasic amino acids from proximal tubule and intestinal lumen, responsible for 1-2% of kidney stones in adults and 6-8% in children [1]. There is at least one risk factor, in 70-80% of the pediatric patients with urolithiasis. These risk factors are metabolic abnormalities, urinary tract infections, or anatomical disorders. Metabolic abnormalities have been reported in approximately 50% of patients [3]. In our patient, cystinuria, a metabolic abnormality, was found to be a risk factor, with no history of the anatomical disorder or urinary tract infection. Since genetic factors may play a role in the etiology of kidney stones, family history should be questioned in patients [4]. In our patient's family history, there were kidney stones in her father, brother, and grandmother. In addition to cystinuria, hypocitraturia was also detected in our patient. Furthermore, a positive nitroprusside test and detection of cystine crystals in the urine are helpful in the diagnosis of cystinuria. Especially the presence of hexagonal cystine crystals in the direct examination of the urine is important to confirm the diagnosis. Therefore, it is important to perform a direct urine examination in patients with urinary system stones. But cystine crystals can only be detected in 20-25% of patients. For this reason, 24-hour urine cystine excretion levels are used for diagnosis [5]. Normally, the excretion of the cystine is 30 mg/day (0.13 mmol/day) in collected urine; in patients with cystinuria, excretion is generally above 400 mg/day (1.7 mmol/day) [6]. In our patient, cystine crystals were found in the direct urine examination. The excretion of spot urine cystine in our patient increased 30 times than normal levels (0.322 mmol/mol creatinine). Two genes were shown to be responsible for cystinuria. According to the genetic classification, mutations in SLC3A1 gene cause type 1 cystinuria; and mutations in SLC7A9 gene cause non-type 1 cystinuria [7]. Our patient, with a c833T>C (p.F278S) homozygous mutation in the SLC3A1 gene, was diagnosed with type 1 cystinuria.

The aim of the treatment of cystinuria is to increase the solubility of the cystine in the urine, decrease the urine concentration, and thereby prevent the formation of new stones. Hydration and dietary measures reduce urine concentration. Urine alkalization increases the solubility of cystine. Pharmacological agents such as D-penicillamine, alpha-mercapto-propionyl-glycine, and captopril enable cystine to turn into more soluble forms. We recommended hydration and sodium-restricted diet to our patient and started potassium citrate treatment. According to the study of Barber F. et al., patients with cystinuria who did not receive treatment need an invasive procedure every 3 years on average [8]. In our patient, invasive treatments for kidney stones were performed 7 times until the age of 16. In addition, since the right kidney was non-functional, nephrectomy was performed. The patient is now followed up in her 1st year after commencing on these treatments and without formation of new stones.

Conclusion

The etiology of the stone should be investigated by further examinations in pediatric patients with recurrent urinary stones. Metabolic abnormalities are common in children with kidney stones. Therefore, metabolic diseases such as cystinuria should be kept in mind in countries where consanguineous marriage

rates are high. Chronic kidney disease and associated morbidity and mortality can be prevented in patients with regular follow-up and treatment that will prevent stone formation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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